groups, histidyl groups, hydroxyl groups, pyridyl groups, anilino groups, morpholinyl groups, thiol groups, and imidazolyl groups, and further wherein about 50 percent or more of the target protein or peptide in an aqueous medium binds to the resin when the aqueous medium has either a high or low ionic strength.

56. (Once Amended) A resin-protein/peptide complex which comprises a resin and a target protein or peptide bound thereto wherein said resin comprises

a) a solid support matrix having a selected ionizable functionality incorporated into the backbone thereof wherein the ionizable functionality is selected such that the resin is electrostatically uncharged at a high and a low ionic strength at the pH where the target protein or peptide is bound to the resin wherein the protein or peptide binds to the resin at a pH or 5 to 9 and is electrostatically charged at the pH where the target protein or peptide is desorbed from the resin, wherein desorption occurs by a change in the pH from the binding pH, and further wherein said ionizable ligand is selected from group consisting of amine groups, phenolic groups, histidyl groups, hydroxyl groups, pyridyl groups, anilino groups, morpholinyl groups, thiol groups, and imidazolyl groups; and

b) optionally a non-ionizable ligand covalently attached thereto,

wherein about 50 percent or more of the target protein or peptide in an aqueous medium binds to the resin when the aqueous medium has either a high or low ionic strength.

REMARKS

Entry of this Amendment and Reply is proper under 37 C.F.R. § 1.116 because the Amendment and Reply places the application in condition for allowance for the reasons discussed herein; does not raise any new issue requiring further search and/or consideration because the Amendment and Reply amplifies issues previously discussed throughout prosecution; does not present any additional claims; and places the application in better form for an appeal should an appeal be necessary. The Amendment and Reply is

necessary and was not earlier presented because it is made in response to arguments raised in the final rejection.

In addition, and for the reasons noted below, Applicants maintain that the finality of the June 21, 2002 Office Action is improper, and, hence, submit that these amendments should be entered as a matter of right under 37 C.F.R. § 1.111.

Entry of the Amendment and Reply, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are thus respectfully requested.

I. CLAIM STATUS AND AMENDMENTS

As correctly indicated in the Office Action Summary, claims 1-5, 7-23, 55, and 56 are pending in this application. Applicants acknowledge the Examiner's renumbering of claims 24 and 25 that were added in the March 27, 2002 Supplemental Amendment to claims 55 and 56. See June 21, 2002 Office Action, page 2.

By the present amendment, claims 1, 16, 55, and 56 have been amended to further clarify Applicants' invention. Support for these amendments can be found in the Specification, at least, at page 27, lines 1-3, page 28, lines 6-9, and at page 30, lines 1-5. Thus, no new matter has been added by these amendments. Applicants submit that none of these amendments are intended to narrow the scope of any element of the claims.

II. DOUBLE PATENTING REJECTION

Claims 1-5, 7-23, 55, and 56 have been rejected under the judicially created doctrine of double patenting over claims 1-13 and 26 -28 of Burton et al. U.S. Patent 5,652,348. See June 21, 2002 Office Action, page 3.

Applicants respectfully traverse this rejection. Applicants note that the present application (i.e., 08/468,610) is a Divisional Application of Application Serial No. 08,268,178 (the '178 application). Applicants cited the '178 application during the prosecution of Application Serial No. 08/311,100 (now U.S. 5,652,348 -- '100 application). August 29, 1995 Amendment, page 11. A copy of the August 29, 1995 Amendment is attached hereto. After citing the copending application, the Examiner in charge of the '100 application did not make a double patenting rejection between the claims of the parent (i.e., the '178 application) of the current application and the claims of the '100 application that issued into U.S. 5,652,348. Thus, it would seem that the Office did not consider the claims of the '178 application (i.e, the parent of the current application) to be material to the patentability of the claims of the '100 application that issued into U.S. 5,652,348.

A review of the prosecution file histories of these applications reveals that the present claims in this application and the issued patent are basically the same as they were when the Office deemed it unnecessary to issue a double patenting rejection. Based on the Office's prior assessment that a double patenting rejection was <u>**not**</u> required, it is unclear as to why the current Examiner now applies one. In fact, this prior assessment would seem to suggest that the claims of this patent are not material to the patentability of the claims the current application. Moreover, the '100 application was filed approximately 3 months after the priority date for this application and, accordingly, is not prior to this application. In view of the above, Applicants submit this double patenting rejection is in error. Thus, Applicants respectfully request the withdrawal of this rejection.

III. CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, NEW MATTER

Claims 55 and 56 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the art that Applicant had possession of the claimed invention. The Examiner asserts that the Specification fails to teach that the

ionizable ligand includes hydroxyl and thiol groups. The Examiner believes that the Specification at the paragraph bridging pages 14-15 indicates that these two groups are reactive functionalities, instead of ionizable ligands. See June 21, 2002 Office Action, pages 3-4.

Applicants respectfully traverse this rejection. It is well understood in the art of protein chromatography that thiol groups and hydroxyl groups are ionizable groups. Ionization depends on the nature of the hydroxyl/thiol group and/or the nature of the molecule containing the thiol/hydroxyl group. This, in turn, depends on how strong the conditions need to be to achieve ionization. For example, phenolics (which are a "sub-family" of hydroxyl ligands) will generally ionise with biocarbonate, while others might require sodium hydroxide. In this regard, the Specification at page 15 even lists phenolics as an ionizable (hydroxyl) group. In addition, thiols, as a class, are easier to ionize than hydroxyls. Thus, it is clear that thiol groups and hydroxyl groups are ionizable groups.

Further support for the inclusion of thiol and hydroxyl groups as ionizable groups can be found in the Specification, at least, at page 24, lines 5-10. Here the Specification teaches the attachment of thiol containing ligands to an epoxide activated solid support matrix. Support for the inclusion of these groups can also be found, at least, in the Specification at page 23, Table 1. This table indicates that hydroxyl and thiol groups are "reactive groups" of or on the ligand. The term ionizable ligand as used throughout this application means any ligand that can be ionised after it is immobilized on the matrix. Since thiol groups and hydroxyl groups are ionizable groups, any immobilized ligand that has a thiol or a hydroxyl group hanging off of it is ionizable.

Thus, contrary to the Examiner's position, the claimed subject matter was described in the Specification in such a way as to reasonably convey to one skilled in the art that Applicant had possession of the claimed invention. Therefore, Applicants respectfully request the withdrawal of this rejection.

IV. PRIOR ART REJECTIONS

Claims 1, 2, 4, 5, 10-16, 18, 20, 22, and 23 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Boardman et al., NATURE, 171:208-210 (1953) ("Boardman"). See June 21, 2002 Office Action, pages 4-7.

Claims 1-5, 7-23, 55, and 56 also stand rejected under 35 U.S.C. §103(a) as allegedly obviousness over Boardman, Sasaki et al., J. BIOCHEM., 86:1537-1548 (1979) ("Sasaki 1979") and Sasaki et al., J. BIOCHEM., 91:1551-1561 (1982) ("Sasaki 1982") in view of Kunin, Ion Exchange Resins, 34-39 (John Wiley & Sons, Inc., Interscience 1958) ("Kunin"), Topp et al., J. CHEM. SOC., Pt. 2:3299-3303 (1949) ("Topp"), Kitchener, Ion Exchangers In Organic and Biochemistry, 63-64 (Calmon and Kressman eds., Interscience Publishers, Inc. 1957) ("Kitchener") and Guthrie, Ion Exchangers In Organic and Biochemistry, 558-559 (Calmon and Kressman eds., Interscience Publishers, Inc. 1957) ("Guthrie"), and further in view of Hancock et al. U.S. Patent No. 4,401,629 ("Hancock"), Kitamura et al. JP Patent No. 01211543 ("Kitamura"), Tokuyama JP Patent No. 60137441, Kondo et al. JP Patent No. 61033130 ("Kondo"), Imuro et al. U.S. Patent No. 4,950,807, Bruegger U.S. Patent No. 4,810,391, Economy et al. U.S. Patent No. 3,835,072 ("Economy"), and Jones et al. U.S. Patent No. 4,154,676 ("Jones"). See June 21, 2002 Office Action, pages 7-11.

Applicants traverse these rejections and reiterate the arguments set forth in the March 27, 2002 Supplemental Amendment and the January 28, 2002 Reply. Applicants further traverse these rejections in light of the following remarks.

First, as to the rejection under 35 U.S.C. § 102(b), Applicants again submit that Boardman fails to anticipate the claimed invention because the reference fails to teach all of the claimed limitations.

Specifically, central to the claimed invention is the claim recitation that the protein binds to the resin at a **pH of 5 to 9** wherein the resin is **uncharged** and **protein binding occurs** at **high and low ionic strengths.** Boardman clearly does not teach this. In point of fact, Boardman teaches the opposite. Specifically, Boardman states that his Amberlite IRC50 carboxylic acid cation resins are "**uncharged only at very low pHs**." Boardman, at page 209, first column, fourth full paragraph. The Examiner has even admitted to this at page 2 of the September 28, 2001 Office Action, wherein it is stated that "[a]t a low pH the cation exchange media is uncharged and binds the proteins." Based on this recitation, no basis is seen in the Office Action or in Boardman to conclude that Boardman teaches binding a protein to an **uncharged resin in the range of pH 5 to 9** wherein the aqueous medium has either a high and low ionic strength. A pH of 5 to 9 is **not** a "very low pH."

In further support of the fact that Boardman fails to meet the claimed limitations, Applicants previously submitted a Declaration under 37 C.F.R. § 1.132 by Nathaniel T. Becker ("Becker Declaration"), a Declaration under 37 C.F.R. § 1.132 by Simon C. Burton ("Burton Declaration"), and a Declaration under 37 C.F.R. § 1.132 by Dr. Steven M. Cramer ("Cramer Declaration"). All of these individuals have worked extensively in, and are recognized experts, in the field of protein chromatography.[1]

The Becker Declaration discusses the Amberlite IR-50 resin utilized in Boardman. This declaration also explains the product literature for the Amberlite IRC-50 resin that was provided by the manufacturer, Rohm and Haas, Co. (2000) ("Rohm and Haas") See Becker Declaration, Exhibit B.

As set forth in the Becker Declaration, the Amberlite IRC-50 is a weakly acidic cation exchange resin and has a pK value of 6.1, meaning that it is still **50% charged** at pH 6.1. The charged moiety on the resin is a carboxylic acid group within the methacrylic

[1] No issue regarding the expertise of these individuals has been raised by the Office.

acid functionality. Given that the resin is weakly acidic, it retains a partial charge at pH 5, and becomes **fully protonated (neutralized) only at a pH of between 2.5 and 4.0,** depending on the buffer salts present. The Rohm and Haas product literature supports this notion. As evident in Figure 3 of Rohm and Haas, the point of zero net charge is equivalent to the pH at which zero millequivalents of base (KOH) have been applied to the resin, which is represented by where the titration curves intersect the y-axis (pH) at zero on the x-axis (mEq KOH). This will vary slightly depending on the buffer salts, but, at most, is pH 4.0 for pure water. Accordingly, the Becker Declaration highlights the **manufacturer's indication** that the same resin utilized in Boardman remains charged at the pH where it binds the protein. Given the manufacturer's indication that the Boardman resin remains charged at the pH of binding, Boardman fails to meet the elements of the claimed invention.

Likewise, the Burton Declaration also discusses the prior art rejections, and in particular, the Amberlite IRC-50 carboxylate resin utilized in Boardman. This declaration also discusses **experimental titration curve data** generated by Burton for the carboxylate Amberlite CG50 resin. The CG50 carboxylate resin is essentially equivalent to the IRC-50 carboxylate resin except that the beads of the IRC-50 resin are much larger. It is the same resin used in the Sasaki references. The Burton Declaration compares the carboxylate resin titration data with theoretical curves calculated using the Henderson-Hasselbach equation. See Burton Declaration, Exhibit B.

The Burton Declaration supports the argument that the carboxylate resin of the prior art references fails to meet all of the limitations of the claimed invention. The claims of the current application contain the limitations "uncharged" and "a high and low ionic strength." Consequently, there is a requirement that the support be uncharged at high (and low) ionic strength when binding the protein. However, as the Burton Declaration shows, the resin in Boardman fails to meet this limitation. As shown in the experimental titration curve in the Burton Declaration, it appears that the percentage of groups **titrated at pH 5**

is 20%. This is curve is consistent with those found in the cited references. For instance, at high ionic strength, Boardman's data shows that at **least 20% carboxyl groups are unprotonated at pH 5**. This clearly contradicts the argument at page 2 of the September 28, 2001 Office Action wherein it is stated that at a pH value of 5, cytochrome c is tightly bound to the media whose carboxylic groups are said to be uncharged. Thus, according to the **experimental data** in the Burton Declaration, the resin in Boardman remains charged at a pH 5.

In an attempt to refute this point, the Examiner argues that the assertion in the Burton Declaration that Boardman demonstrates that the resin is 20% unprotonated at pH 5 only applies at **high ionic strength**. See June 21, 2002 Office Action, page 6. In this regard, the Examiner asserts that Boardman teaches that at pH 5.0, cytochrome c binds to the resin whereby the resin meets the definition of "electrostatically uncharged" set forth in the Specification for a **low ionic strength**. In this regard, the Examiner relies on Fig. 1a of Boardman as allegedly showing that the carboxylic groups of the resin are **almost wholly undissociated** at pH 5.0. However, this assertion contradicts the overall teaching of Boardman. In reference to Fig 1a, Boardman concludes that the Amberlite IRC50 carboxylic acid cation resins are "**uncharged only at very low pHs**" and not at a pH of 5 to 9. See Boardman, page 209, first column, fourth full paragraph. In this regard, Boardman does not distinguish between high and low ionic strength.

This argument also fails to address the claim recitation requiring binding of the protein at high and low ionic strength. It is not enough that the protein bind at low ionic strength. The claim recitation is only met when the same protein also binds at a high ionic strength.

Furthermore, Boardman fails to define the term "**almost wholly undissociated**." Thus, the reference does not literally read on the limitation "electrostatically uncharged." The Examiner argues that the Specification, at page 18, first full paragraph, indicates that

the term "electrostatically uncharged" is defined as less than 5% (preferably less than 1%) of the ionizable funtionalities on the resin are charged at the binding pH of 5 to 9. Nonetheless, Boardman does not indicate that "almost wholly undissociated" equates to less than 5%, or less than 1%. In fact, Boardman fails to teach what percentage of charge remains on the resin.

Even assuming *arguendo* that the Office is correct (and it is not) in establishing that Boardman binds at low salt, Boardman is insufficient to meet the limitations of the claims. In particular, Boardman fails to meet the claim recitation that requires the resin to be electrostatically uncharged at a high and a low ionic strength at the pH where the protein binds the resin. It is not enough that the protein binds at low ionic strength. The claims are only met when the protein binds at a high ionic strength, as well.

In fact, Applicants submit that the ability of the claimed invention to bind at both a high and a low ionic strength is unique to the claimed invention. This ability effectively solved one of the problems present in the state of the art of protein chromatography at the time of the claimed invention. In particular, the state of the art prior at the time of the claimed invention was such that some chromatographic techniques required extensive salting and desalting of the protein solution. This salting and desalting required the use of large quantities of reagents to effect recovery on industrial scale. See Specification, page 5, lines 4-10 and lines 17-27. Accordingly, this feature distinguishes the claimed invention from the cited prior art.

Moreover, it is well established that to anticipate a claim, a single prior art reference must teach, either expressly or inherently, each and every element of the claimed invention. See M.P.E.P. § 2131; Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). In view of the above discussion, it is apparent that Boardman fails to teach, either expressly or

inherently, each and every claimed limitation. Thus, Boardman cannot be said to anticipate the claimed invention.

Based on the Examiner's arguments at pages 4-6, it would appear that the Examiner is relying on the teachings of Topp, Kunin, and Kitchener, as well as the Henderson-Hasselbach equation as allegedly teaching that the Boardman resin is uncharged at pH 5.0 in low ionic strength. Applicants submit that such reasoning is improper for a rejection under 35 U.S.C. § 102. Applicants further submit that the rejection's reasoning is factually inaccurate.

In this regard, the argument is improper because the claims are rejected under 35 U.S.C. § 102 as allegedly anticipated by Boardman, not under 35 U.S.C. § 103 as allegedly obvious over Boardman in view of Topp, Kunin, and Kitchener. It would appear that the Examiner is arguing that Boardman anticipates the claimed invention when taken in view of Topp, Kunin, and Kitchener. This argument takes the guise of a rejection under 35 U.S.C. § 103 for obviousness. Thus, the argument is improper.

Second, and perhaps more importantly, Applicants submit that Topp, Kunin, and Kitchener, and in fact all of the secondary references, fail to teach or suggest that the Boardman resin is uncharged at pH 5.0 at a high and low ionic strength when it binds the protein.

The Kunin article merely relates to a discussion of titration curves of several ion exchange media, including the titration curve of the carboxylic acid cation exchange resin, Amberlite IR-105. (Kunin, page 37, Figure 13). While it is true that this resin is same resin used in Boardman, this teaching does not remedy the deficiencies of the Boardman reference. Namely, it fails to teach or suggest methods which recover a protein or peptide by binding the protein or peptide from an aqueous solution with a resin, containing an ionizable functionality, which is electrostatically uncharged at physiological pHs of from 5

to 9 and in which proteins are then recovered from the resin merely by changing the pH to effect desorption. The reference is silent with regard to the charge on the resin at high and low ionic strength.

Topp and Kitchener share the same fate as Kunin. With regard to Topp, the Examiner argues that the relevant data is presented in Fig. 2 and discussed at page 3301, wherein it is stated that in the absence of added salt, exchange is neglible at pH's below 6. The Examiner then argues that no added salt satisfies the low ionic strength as required by the claims. See June 21, 2002 Office Action, pages 5-6. However, Topp fails to teach or suggest methods for **recovering proteins by binding the protein to an electrostatically uncharged resin at a high and a low ionic strength** at physiological pHs of from 5 to 9, and in which proteins are then recovered from the resin merely by changing the pH to effect desorption.

Similarly, Kitchener also fails to teach a method for **recovering proteins by binding the protein to an electrostatically uncharged resin at a high and a low ionic strength** at physiological pHs of from 5 to 9, and in which proteins are then recovered from the resin merely by changing the pH to effect desorption..

Finally, regarding the rejection under 35 U.S.C. § 102, the Examiner appears to rely on carboxylate ion exchangers and their pKas. In particular, it appears that the Examiner relies heavily on pKa followed by derivation using the Henderson-Hasselbach equation in view of Boardman, Kunin, Topp, and Kitchener as teaching the claimed invention. See June 21, 2002 Office Action, pages 6 and 7. However, as argued in our previous amendments the Burton Declaration proves that the **experimental titration curves** disclosed in the above-cited references, in particular Kunin, Kitchener, Rohm and Haas, plus the carboxylate titration curve generated in the Burton Declaration do not fit the theoretical titration curves calculated using the simple Henderson-Hasselbach equation.

The Burton Declaration indicates that pKa data is irrelevant except for theoretical calculation of the percentage of protonated carboxyl groups using the Henderson-Hasselbach equation. This equation states that the ratio of protonated to unprotonated carboxyl groups is 1 at pH equal to the pKa; 10 at pH 1 unit below the pKa; and 0.1 at pH 1 unit above the pKa. Thus, about 90% of the titration curve should lie between the values of 1 unit either side of the pKa. The titration curves in Kunin, Kitchener, Rohm and Haas, and the carboxylate titration curve in the Burton Declaration do **not** fit this. Instead, the titration range is broader, probably due to heterogeneity and neighboring group effects in a polyvalent species such as an ion exchanger. Thus, the **experimental titration data** discussed in the Burton Declaration makes it evident that titration of protonated carboxylates starts before pH 5.

Additionally, the Cramer Declaration submitted along with the March 27, 2002 Supplemental Amendment supports the conclusion that the prior art references neither teach nor suggest binding to an uncharged resin between pH 5 and 9 at high and low ionic strength. As set forth in the Cramer Declaration, the Amberlite IRC-50 is a weakly acidic cation exchange resin which becomes fully protonated at a pH of 2.5 to 4.0 depending on the buffer salts present. Upon reviewing the titration data supplied by the manufacturer in the reference by Kunin, in the Rohm and Haas product literature, and in the data of the Burton Declaration, the Cramer Declaration concludes that the Amberlite IRC-50 carboxylate resins remain charged at pH 5 and are not fully protonated until the pH is **less than 4.0**. The Cramer Declaration even sets forth that typical weak cation exchangers used in the biotechnology industry (e.g., CM-Sephadex) have pKa's in the 3.5 to 4 range, thus requiring a low pH to become fully protonated and uncharged.

The Cramer Declaration further indicates that it is good practice to use **experimental titration data** rather than theoretical calculations to determine the charged state of ion exchange resins. In particular, the Cramer Declaration asserts that the carboxylate titration data found in the Burton Declaration confirms that the pKa is

irrelevant except for theoretical calculations of the percentage of protonated carboxyl groups using the Henderson Hasselbach equation. Moreover, the Cramer Declaration indicates that these theoretical considerations should not take the place of experimental data.

Nonetheless, the Examiner in one sentence summarily dismissed the Cramer Declaration as allegedly adding only a "concurring opinion, and no further data." See June 21, 2002 Office Action, page 7. Applicants submit that this dismissal is in error. Factually based expert opinions are entitled to consideration. See M.P.E.P. § 716.01(c); In re Carroll, 601 F.2d 1184, 202 U.S.P.Q. 571 (C.C.P.A. 1979). The Cramer Declaration adds more than mere conclusory statements. The Cramer Declaration uses sound scientific reasoning to accurately explain the factual experimental titration curves of Burton and the prior art. It is well established that an Examiner must consider all evidence of patentability that is presented during rebuttal. See In re Eli Lilly & Co., 902 F.2d 943, 945, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990). Accordingly, the one sentence summary dismissal of the Cramer Declaration is improper.

Thus, for the reasons noted above, Boardman fails to teach each and every element of the claimed invention. Accordingly, Boardman fails to anticipate the claimed invention. Applicants request the withdrawal of this rejection.

Turning to the rejection under 35 U.S.C § 103(a), Applicants note that this case previously went up on appeal to the Board of Patent Appeals and Interferences ("Board") over an obviousness rejection utilizing a combination of references that includes the same two Sasaki articles (utilized once again as primary references) that the Examiner uses now. Resolving this prior Appeal, the Board found that the Sasaki references do not obviate nor anticipate the claimed invention.

In particular, the Board found that each Sasaki reference "lacks performing the process with a resin that undergoes the transition between uncharged and charged between pH values of 5 to 9." May 31, 2001 Decision on Appeal, pages 4-5. According to the Board, "neither Sasaki reference describes a resin which meets the requirements of the claims on appeal." May 31, 2001 Decision on Appeal, page 5. Thus, the Board held that the Sasaki articles were not pertinent to the claimed invention, because neither one discloses or suggests methods which recover protein or peptides by binding the protein or peptides to a electrostatically uncharged resin at physiological pHs of from 5 to 9 after which the protein or peptides are then recovered from the resin merely by changing the pH to effect desorption. This failure of Sasaki to suggest such resins is even recognized in the September 28, 2001 Office Action at pages 4-5 ("Sasaki et al. lack forming the complex with a resin that is uncharged between pH values of 5-9."). For this reason alone, Applicants submit that the Sasaki references are no more applicable to the rejection now than they were when the Board found that they did not anticipate or obviate the claimed invention.

Furthermore, in addition to Sasaki's failing to disclose or suggest the limitations of the claims, Applicants believe that these references in fact "teach away" from the claimed invention. Specifically, the cited Sasaki articles lead to the conclusion that the employed ionizable Amberlite CG-50 resins are **charged** at any pH within the claimed pH range from 5 to 9, because the Sasaki articles indicate that a **pH of 4.5 or less** is required to completely protonate the carboxyl groups of the resins. Accordingly, at a pH of 5 or more, Sasaki's Amberlite CG-50 resins would carry an anionic charge. Sasaki recognized this limitation at page 1561 of his 1982 article where he states that:

> "However, hydrophobic-ionic chromatography with Amberlite CG-50 has the disadvantage that a pH as acidic as 4.5 is required in the process of adsorption."

As such, both Sasaki references are limited to Amberlite resins which would bind the protein or peptides at pHs of 4.5 or less. This clearly leads one of ordinary skill in the art

away from the claimed invention which calls for the use of **uncharged resins** that bind proteins in a medium with a **pH of 5 to 9**.

It is well established that a prior art teaching must be considered as a whole including portions that "teach away" from the claimed invention. See M.P.E.P. § 2141.02; W.L. Gore & Associates, Inc., v. Garlock, Inc., 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Moreover, references cannot be combined where the references teach away from their combination. M.P.E.P. § 2145; In re Grasselli, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983).

Given Sasaki's teaching away, the Sasaki references cannot now be properly combined with the remaining references to arrive at the claimed invention. In addition, such a teaching away also means that the references clearly fail to provide a reasonable expectation to one of ordinary skill in the art of successfully arriving at the claimed invention upon a reading of the prior art. Nonetheless, the Examiner has chosen to disregard this teaching away of the prior art.

Therefore, the Sasaki articles would not provide the requisite motivation to the skilled artisan to employ ionizable functionalities which would dissociate at pHs of from 5 to 9. In view of these arguments, the two Sasaki references, alone, or in combination with each other, in combination with Boardman or in combination with any of the cited secondary references (discussed more fully below) do not render obvious the claimed invention. Applicants again remind the Office that each of these points regarding both Sasaki references were already successfully argued to the Board in the prior appeal in this case.

As to Boardman (the other primary reference), Applicants submit that the teachings of Boardman, Kunin, Topp, and Kitchener have been discussed above. To reiterate, Boardman does not obviate or anticipate the now presented claims. In particular, the

reference fails to teach binding of the protein at a pH of 5 to 9 and further fails to teach that the resin is uncharged at such pHs. As already discussed above, the September 28, 2001 Office Action admits to this at page 2 wherein it states that "at a low pH the cation exchange media is uncharged and binds the proteins."

Morever, Applicants submit that Boardman is even further removed from the claimed invention than Sasaki which the Board maintained did not obviate or anticipate the now presented claims. As previously discussed, Sasaki disclosed that the Amberlite CG-50 resin was uncharged only at pHs of about 4.5 or less. Boardman states that his resins are uncharged only at "very low pHs." Boardman, page 209, first column, fourth full paragraph. Based on this recitation, one skilled in the art cannot reasonably conclude that a very low pH reads of pHs from 5 to 9. Accordingly, the teaching of Boardman is contrary to the claimed invention.

Boardman clearly **teaches away** from the claimed method, which requires binding of the protein in a medium to an electrostatically uncharged resin wherein said medium has a pH of 5 to 9. Given this teaching away, the Boardman reference cannot be properly combined with the secondary references to arrive at the claimed invention. In addition, such a teaching away also means that the reference completely fails to provide a reasonable expectation to one of ordinary skill in the art of successfully arriving at the claimed invention. Nonetheless, the Examiner has chosen to ignore this teaching away from the claimed invention.

Therefore, the Boardman reference, alone, or in combination with the Sasaki references or in combination with any of the cited secondary references (discussed more fully below) does not render obvious the claimed invention.

The secondary references of Kunin, Topp, Kitchener have been discussed above. For the reasons noted above, these references fail to remedy the above-noted deficiencies

of the primary references. Applicants submit that the additional secondary references of Guthrie, Hancock, Kitamura Tokuyama Kondo, Imuro, Bruegger, Economy, and Jones also fail to remedy the above-noted deficiencies of the primary references.

The Guthrie reference merely lists the pH at half capacity for a number of ion exchange cotton fabrics. According to Table I in Guthrie, the various modifying groups have pH at half capacity ranging from 1.5 to 12. The Examiner relies on the additional secondary references of Hancock, Kitamura Tokuyama Kondo, Imuro, Bruegger, Economy, and Jones as allegedly teaching polymeric ion exchange resins, which according to the Examiner, **may** contain various ionizable functional groups, such as pyridyl groups, phenolic groups, hydroxyl groups, amino groups, and morpholino groups. However, these references fail to teach or suggest methods which recover proteins by binding the protein from an aqueous solution with a resin, containing an ionizable functionality, which is electrostatically uncharged at physiological pHs of from 5 to 9 and in which proteins are then recovered from the resin merely by changing the pH to effect desorption at a high and low ionic strength.

The Examiner has relied on these secondary references as allegedly disclosing media with "ionizable ligands" which can be used in the claimed pH range of 5 to 9. However, as argued in our previous amendments, this amounts to nothing more than to an "obvious to try" rationale to arrive at the claimed method steps. The rejection utilizes multiple references providing numerous possible choices. However, none of the references give direction as to which parameters are crucial nor do they indicate which one of the many possibilities is likely to succeed. In moving from the prior art to the claimed invention, one cannot base a determination of obviousness on what one of ordinary skill in the art might try or find obvious to try. In re O'Farrel, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Indeed, the proper test requires determining what the prior art would have led the skilled artisan to do. However, each of the cited secondary

references fails to teach or suggest the elements of the claimed methods. Hence, the secondary references fail to cure the deficiencies of the primary references.

Even more to the point, none of the references either alone or in combination suggest that recovery of proteins can be achieved at high and low ionic strength.

Therefore, nothing in the cited prior art references teaches or suggests the elements of the claimed invention. Nor do these references, either alone or in combination, provide a reasonable expectation of success to a skilled artisan that the modifications necessary to the prior art references to arrive at the claimed invention would be successful in effecting protein recovery. Absent such suggestion and reasonable expectation of success, this rejection is believed to be error. In re Vaeck, 947 F.2d at 488, 20 U.S.P.Q.2d at 1438.

Finally, the mere fact that the Examiner had to combine **fifteen** references in an attempt to arrive at the claimed invention is indicative of the non-obviousness of the claimed invention.

Thus, for the reasons noted above, Applicants respectfully request the withdrawal of this rejection.

V. REQUEST FOR WITHDRAWAL OF FINALITY

Applicants note that several substantive errors were made in the Examiner's issuance of the June 21, 2002 Office Action.

The Examiner indicated that Applicants' action necessitated the new ground of rejection under the judicially created doctrine of double patenting based on Applicant's own issued patent, U.S. Patent No. 5,652,348 issued to Burton et al. ("Burton '348"). See June 21, 2002 Office Action, page 10. One could construe that the Office Action implied that Applicants' failure to disclose this patent to the Office contravenes the duty to

disclose under 37 C.F.R. § 1.56, and that as a consequence, the Office should not benefit the Applicants with a non-final Office Action. See June 21, 2002 Final Office Action, pages 10-11.

Applicants submit that any such construction is in error. Contrary to the Examiner's position, Applicants have complied with the duty of disclosure under 37 C.F.R. § 1.56 with regard to U.S. Patent No. 5,652,348 and the current application. As noted above, the present application (i.e., 08/654,937) is a File Wrapper Continuation of Application Serial No. 08,268,178. The '178 application was cited during the prosecution of Application Serial No. 08/311,100, now U.S. 5,652,348. See Application Serial No. 08/311,100, August 29, 1995 Amendment, page 11. Applicants note that the Examiner of the '100 application did not make a double patenting rejection between the claims of these applications. Thus, it would appear that the Office did **not** consider the '178 application (i.e., the parent of the current application) to be "material to the patentability" of the '100 application that issued into U.S. 5,652,348. Under 37 C.F.R. § 1.56, Applicants are only required to disclose information that is "material to patentability."

A review of the prosecution file histories of the current application (which is a divisional from the parent), which contains the same file history of Application Serial No. 08/268,178, and Application Serial No. 08/311,100, now U.S. 5,652,348, reveals that the claims in these applications and the issued patent are basically the same as they were when the Office deemed it unnecessary to issue a double patenting rejection. Given the Office's prior assessment that the claims of the '178 application **were not material to the patentability** to the claims of the '100 application, Applicants submit that the Burton patent is **not** information that is **material to patentability** of the current application.

Accordingly, the Examiner's implication that Applicants' failure to disclose the Burton patent to the Office contravenes the duty to disclose under 37 C.F.R. § 1.56 is a gross and unjust mis-characterization of Applicants. Similarly, the Examiner's assertion

that the Office should not benefit the Applicants with a non-final Office action for this alleged conduct is an unjust use of the Office's power. For at least this reason, the finality of the June 21, 2002 Office Action should be withdrawn, and Applicants hereby request such action.

Second, even assuming *arguendo* that Applicants were required to disclose the Burton '348 patent to the Office, Applicants submit that the finality of the June 21, 2002 Office Action is premature. In reference to the alleged reasons necessitating the new grounds of rejection, the Examiner stated that the newly submitted claims required the addition of new references (eight new references) establishing that such resins were known in the art. See June 21, 2002 Office Action, page 11. However, Applicants did not amend any of the claims to which the newly cited references now apply. Thus, the June 21, 2002 Office Action applies eight new references against claims that were not amended.

Thus, the Examiner's statement that "[t]he newly submitted claims required the addition of references establishing that such resins were known in the art" is in error. Contrary to the position taken by the Examiner, the new claims did not necessitate the addition of new references to the rejection under 35 U.S.C. § 103(a). Section 706.07(a) of the M.P.E.P. provides the following:

> Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is **neither necessitated by applicant's amendment of the claims** nor based on information submitted in an information disclosure statement filed during the period set forth in 37 C.F.R. § 1.97(c) with the fee set forth in 37 C.F.R. § 1.17(p). Where information is submitted in an information disclosure statement during the period set forth in 37 C.F.R. § 1.97(c) with a fee, the examiner may use the information submitted, e.g., a printed publication or evidence of public use, and make the next Office action final whether or not the claims have been amended, provided that **no other new ground of rejection which was not necessitated by amendment to the claims is introduced by the examiner**. [Emphasis added.]

Since the new claims did not necessitate the additional references, the addition of the these extra references to the rejection under 35 U.S.C. § 103(a) constitutes a new grounds of rejection **not necessitated** by the new claims. Thus, the finality of the Office Action is premature. Applicants request the withdrawal of the finality of the June 21, 2002 Office Action.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: [signature]

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ATTACHMENT TO AMENDMENT AND REPLY

Marked-up Copy of Amended Claims 1, 16, 55, and 56

([bracketed] items deleted; underlined items added)

1. (Thrice Amended) A resin-protein/peptide complex which comprises a resin and a target protein or peptide bound thereto wherein said resin comprises

a) a solid support matrix; and

b) selected ionizable ligand covalently attached to the matrix.

wherein the ionizable ligand is selected such that the resin is electrostatically uncharged at a high and a low ionic strength at the pH where the target protein or peptide is bound to the resin wherein the protein or peptide binds to the resin at a pH of 5 to 9 and is electrostatically charged at the pH where the target protein or peptide is desorbed from the resin wherein desorption occurs by a change in the pH from the binding pH and further wherein about 50 percent or more of the target protein or peptide in an aqueous medium binds to the resin when the aqueous medium has either a high or low ionic strength.

16. (Thrice Amended) A resin-protein/peptide complex which comprises a resin and a target protein or peptide bound thereto wherein said resin comprises

a) a solid support matrix having a selected ionizable functionality incorporated into the backbone thereof wherein the ionizable functionality is selected such that the resin is electrostatically uncharged at a high and a low ionic strength at the pH where the target protein or peptide is bound to the resin wherein the protein or peptide binds to the resin at a pH or 5 to 9 and is electrostatically charged at the pH where the target protein or peptide is desorbed from the resin wherein desorption occurs by a change in the pH from the binding pH; and

b) optionally a non-ionizable ligand covalently attached thereto,

wherein about 50 percent or more of the target protein or peptide in an aqueous medium binds to the resin when the aqueous medium has either a high or low ionic strength.

55. (Once Amended) A resin-protein/peptide complex which comprises a resin and a target protein or peptide bound thereto wherein said resin comprises

a) a solid support matrix; and

b) selected ionizable ligand covalently attached to the matrix,

wherein the ionizable ligand is selected such that the resin is electrostatically uncharged at a high and a low ionic strength at the pH where the target protein or peptide is bound to the resin wherein the protein or peptide binds to the resin at a pH of 5 to 9 and is electrostatically charged at the pH where the target protein or peptide is desorbed from the resin wherein desorption occurs by a change in the pH from the binding pH, and wherein said ionizable ligand is selected from group consisting of amine groups, phenolic groups, histidyl groups, hydroxyl groups, pyridyl groups, anilino groups, morpholinyl groups, thiol groups, and imidazolyl groups, and further wherein about 50 percent or more of the target protein or peptide in an aqueous medium binds to the resin when the aqueous medium has either a high or low ionic strength.

56. (Once Amended) A resin-protein/peptide complex which comprises a resin and a target protein or peptide bound thereto wherein said resin comprises

a) a solid support matrix having a selected ionizable functionality incorporated into the backbone thereof wherein the ionizable functionality is selected such that the resin is electrostatically uncharged at a high and a low ionic strength at the pH where the target protein or peptide is bound to the resin wherein the protein or peptide binds to the resin at a pH or 5 to 9 and is electrostatically charged at the pH where the target protein or peptide is desorbed from the resin, wherein desorption occurs by a change in the pH from the binding pH, and further wherein said ionizable ligand is selected from group consisting of amine groups, phenolic groups, histidyl groups, hydroxyl groups, pyridyl groups, anilino groups, morpholinyl groups, thiol groups, and imidazolyl groups; and

b) optionally a non-ionizable ligand covalently attached thereto,

wherein about 50 percent or more of the target protein or peptide in an aqueous medium binds to the resin when the aqueous medium has either a high or low ionic strength.